70. The method of producing a chemokine-like factor polypeptide comprising introducing the vector of Claim 67 into a host cell, and expressing from the host cell or extracellular media the polypeptide encoded by said cDNA.

71. The method of Claim 70, wherein the host cell is one member selected from the group consisting of bacterium, and animal cell.

72. The polynucleotide of Claim 64, wherein the polynucleotide is RNA.

REMARKS

I. Restriction Requirement and New Pending Claims

Claims 6-8, 11-13 and 17-33, have been withdrawn without prejudice, as being drawn to a non-elected group invention in response to the Examiner's Restriction Requirement. The remaining pending claims are 1-5, 9-10 and 14-16.

To facilitate examination of the remaining pending claims, Applicant cancels remaining pending claims 1-5, 9-10 and 14-16, without prejudice, in favor of new pending claims 34 through 72.

Please note that new Claim 34 corresponds to portions of cancelled pending Claim 1 (Claim 1a and 1b), new Claim 51 corresponds to a portion of cancelled pending Claim 1 (Claim 1g), new Claim 64 corresponds to portions of cancelled pending Claim 1 (Claim 1f and 1h), and the remaining new claims are comparable in scope with the other cancelled pending claims.

There are totally 39 new claims, with three independent claims (Claims 34, 51 and 64). The instant patent application as filed has 33 claims. Applicants submitted the filing fee including the fee for claims in excess of twenty. Applicants submit herein a check in amount of $54 for six additional claims.

II. Sequence Compliance

Applicants have obviated the Examiner's objection of failure to comply with the requirements of 37 CFR 1.821-1.825 by following two actions:

(1) Applicants have added the primer sequences (primer 1, 2, 1', 2' and 5), described on page 23, 24 and 25 as filed, into the Sequence Listing. Applicants resubmit herein the Sequence Listing including the five primer sequences in both hard copy and electronic file.

(2) Applicants insert relevant sequence identifiers on page 23, line 13-14, page 24, lines 32-33; and page 25, line 28.

Applicants appreciate the Examiner's assistance in obviating this matter.

III. Information Disclosure Statement

Applicants are submitting the missing copies of the references from the original Information Disclosure Statement.

IV. Drawings

The Examiner has objected to the graphs in Figures 5A-5C and 5H-5I. Accordingly, Applicants are submitting corrected Figures 5A-5C and 5H-5I to obviate this objection.

V. Specification

A. Applicants have deleted the hyperlinks contained in the Specification to obviate the Examiner's objection based upon the MPEP §608.1

B. Applicants have changed the title of the patent application as suggested by the Examiner to obviate the Examiner's objection.

VI. Claims

A. Item 6:

The claims were objected to as being drawn to a non-elected invention. This objection is obviated by new pending claims 34 through 72 that are drawn to the elected invention.

B. Item 7:

Cancelled pending Claims 1-5, 9-10 and 14-16 were rejected under 35 U.S.C. 112, first paragraph. This rejection is obviated by new pending Claims 34-63. More specifically, as suggested by the Examiner, new pending Claims 34-63 have not included the terms "naturally occurring variant" and "85% identical" language of cancelled pending Claim 1(f) and 1(h).

Pending Claims 64-72 include the terms "variant" and "85% identical" language of cancelled pending Claim 1(f) and 1(h) and therefore stand rejected under 35 U.S.C. 112, first paragraph. The Examiner maintains that the Specification does not enable one skilled in the pertinent art to make and use the invention commensurate in scope with these claims. This rejection is respectively traversed.

The Examiner maintains that undue experimentation would be required to obtain an allelic variant of the claimed isolated polynucelotide. Similarly the Examiner maintains that undue experimentation would be required to obtain an isolated polynucelotide that is 85% identical to the claimed isolated polynucelotide. In both instances, undue experimentation is not applicable.

In the case of the variant of the isolated polynucelotide, the Specification provides (emphasis being added for convenience) that:

> [0049] The present invention further relates to variants of the hereinabove described polynucleotides which encode for fragments, analogs and derivatives of the polypeptide having the deduced amino acid sequence selected from the group consisting of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8 or the polypeptide encoded by the cDNA of the

deposited clone. The variant of the polynucleotides may be a naturally occurring allelic variant of the polynucleotide or a non-naturally occurring variant of the polynucleotide.

[0050] Thus, the present invention includes polynucleotides encoding the same mature polypeptide as shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8 or the same mature polypeptide encoded by the cDNA of the deposited clone as well as variants of such polynucleotides which variants encode for a fragment, derivative or analog of the polypeptide of SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8, or the polypeptide encoded by the cDNA of the deposited clone. Such nucleotide variants include deletion variants, substitution variants and addition or insertion variants.

[0051] As indicated above, the polynucleotide may have a coding sequence which is a naturally occurring allelic variant of the coding sequence shown in SEQ ID NO:2, SEQ ID NO:4, SEQ ID NO:6, SEQ ID NO:8 or of the coding sequence of the deposited clone. As known in the art, an allelic variant is an alternate form of a polynucleotide sequence which may have a substitution, deletion or addition of one or more nucleotides, which does not substantially alter the function of the encoded polypeptide.

From the Specification, it is readily apparent that a variant encode for a fragment, derivative or analog of the polypeptide of SEQ ID NO:2 and that a fragment, derivative or analog of the polypeptide of SEQ ID NO:2 means a polypeptide which retains essentially the same biological function or activity as the polypeptide. Moreover, the Specification further teaches that the fragment, derivative or analog of the polypeptide can be readily obtained by methods known to those skilled in the art. Therefore, it is not incumbent on Applicant to teach each and every variant since those skilled in the art know how to make such variants. Applicant is not required to teach that which is known. There is no undue experimentation to perform that which is known in the art. Moreover, Applicant has particularly pointed out and distinctly claimed the variants such that one skilled in the pertinent art understands the metes and bounds of the claimed invention. Consequently, when one skilled in the art makes a variant of the claimed isolated polynucelotide by commonly known methods, the claims sufficiently apprise the skilled artisan of whether such variant is within the scope of the claimed invention.

In the case of 85% identity, the Specification provides that:

> [0056] Fragments of the full length CKLFs gene may be used as a hybridization probe for a cDNA library to isolate the full length CKLFs gene and to isolate other genes which have a high sequence similarity to the gene or similar biological activity. Probes of this type preferably have at least 30 bases and may contain, for example, 50 or more bases. The probe may also be used to identify a cDNA clone corresponding to a full length transcript and a genomic clone or clones that contain the complete CKLF gene including regulatory and promoter regions, exons, and introns. An example of a screen comprises isolating the coding region of the gene by using the known DNA sequence to synthesize an oligonucleotide probe. Labeled oligonucleotides having a sequence complementary to that of the gene of the present invention are used to screen a library of human cDNA, genomic DNA or mRNA to determine which members of the library the probe hybridizes to.
>
> [0057] The present invention further relates to polynucleotides which hybridize to the above-described CKLF1 sequence if there is at least 85%, preferably at least 90%, and more preferably at least 95% identity between the sequences.
>
> [0058] Alternatively, the polynucleotide may have at least 20 bases, preferably 30 bases, and more preferably at least 50 bases which hybridize to the CKLF1 polynucleotide of the present invention and which has an identity thereto, as hereinabove described, and which may or may not retain activity. For example, such polynucleotides may be employed as probes for the polynucleotide of SEQ ID NO:1, for example, for recovery of the polynucleotide or as a diagnostic probe or as a PCR primer.
>
> [0059] Thus, the present invention is directed to polynucleotides having at least a 85% identity, preferably at least 90% and more preferably at least a 95% identity to a CKLF1 polynucleotide which encodes the polypeptide of SEQ ID NO:2 as well as fragments thereof, which fragments have at least 30 bases and preferably at least 50 bases and to polypeptides encoded by such polynucleotide.

It is readily apparent that those skilled in the art are able to obtain fragments of the claimed isolated polynucelotide. Therefore, it is not incumbent on Applicant to teach how to make each and every polynucleotide which has at least 85% identity to a CKLF1 polynucleotide which encodes the polypeptide of SEQ ID NO:2, or a polynucleotide encoding a mature polypeptide having the amino acid sequence

expressed by the cDNA contained in CGMCC Deposit NO.0392 of the present invention. Applicant is not required to teach that which is known. There is no undue experimentation to perform that which is known in the art. In addition, Applicants have provided utilities for the claimed polynucelotide having at least 85% identity. Moreover, Applicants have particularly pointed out and distinctly claimed the isolated polynucelotide such that one skilled in the pertinent art understands the metes and bounds of the claimed invention. Consequently, when one skilled in the art makes the claimed polynucelotide having at least a 85% identity, the claims sufficiently apprise the skilled artisan of whether such polynucelotide is within the scope of the claimed invention.

Accordingly, Applicant respectfully requests withdrawal of the rejection based upon 35 U.S.C. §112, first paragraph.

C. Item 8:

Cancelled pending Claims 1-5, 9-10 and 14-16 were rejected under 35 U.S.C. 112, first paragraph. This rejection is obviated by new pending Claims 34-72.

More specifically, new pending Claims 34-63, as stated by the Examiner in the instant Office Action (page 11, last paragraph), meet the written description provision under 35 U.S.C. 112, first paragraph. Pending Claims 64-72 include the terms "variant" and "85% identical" language of cancelled pending Claim 1(f) and 1(h) and therefore stand rejected under 35 U.S.C. 112, first paragraph. This rejection is respectively traversed.

Applicants desire to point out that Claim 64 is directed to a polynucleotide, which is at least 85% identical to the polynucleotide encoding the polypeptide consisting of the amino acid sequence as set forth in SEQ ID NO:2 (part i), and a polynucleotide encoding a mature polypeptide having the amino acid sequence expressed by the cDNA contained in CGMCC Deposit 0392 (part ii). While it is true that the specification teaches a human chemokine-like factor polynucleotide (SEQ ID NO:1) and a polypeptide encoded by the nucleotides of SEQ ID NO:1, it is not proper to require Applicant to disclose each and every functionally equivalent polynucleotides and

polypeptides which incorporate all variants and fragments. Applicants specifically defined in the Specification that fragments, derivatives or analogs of the polypeptide of CKLF means a polypeptide which retains essentially the same biological function or activity as such polypeptides (page 10, line 24-29 of the Specification). As noted, fragments, derivatives or analogs of the polypeptide of CKLF can be obtained by those skilled in the art by such well known techniques as substitution, fusion and splice variants.

Moreover, Applicants appreciate that certain positions in the sequence are critical to the protein's structure and function relationship. However, Applicants also teach in the Specification, at page 9, lines 12-17 that whether or not the polynucleotide may or may not retain activity, the polynucleotide may be employed as probes for the polynucleotide of SEQ ID NO:1, for example recovery of the polynucleotide or as a diagnostic probe or as a PCR primer. Applicants have sufficiently described the polynucleotide and the polynucleotide that is at least 85% identical to the original polynucleotide meets the written description requirements.

Accordingly, Applicant respectfully requests withdrawal of the rejection based upon 35 U.S.C. §112, first paragraph.

D. Item 9

Cancelled pending Claims 1-5, 9-10 and 14-16 were rejected under 35 U.S.C. 112, first paragraph. This rejection is obviated by new pending Claims 34-72 and the Declaration Of Biological Culture Deposit signed by an inventor of the present invention. Accordingly, Applicant respectfully requests withdrawal of the rejection based upon 35 U.S.C. §112, first paragraph.

E. Item 10

Cancelled pending Claims 1-4, 9-10 and 14-16 were rejected under 35 U.S.C. 103 (a) as being unpatentable over NCI-CGAP (Genbank Accession NO. A1078580) in view of Hillier et al. (Genbank Accession No. AA455042) and Sibson et al. (WO

94/01548). This rejection is respectfully traversed by new pending Claims 34-70 and the following remarks.

Applicants claim in Claim 34 an isolated polynucleotide comprising a member selected from the group consisting of (a) a polynucleotide encoding the polypeptide consisting of the amino acid sequence as set forth in SEQ ID NO:2; (b) a polynucleotide encoding a mature polypeptide having the amino acid sequence expressed by the cDNA contained in CGMCC Deposit NO.0392. Applicants further claim in Claim 51 an isolated polynucleotide capable of hybridizing to (a) a polynucleotide encoding the polypeptide consisting of the amino acid sequence as set forth in SEQ ID NO:2; or (b) a polynucleotide encoding a mature polypeptide having the amino acid sequence expressed by the cDNA contained in CGMCC Deposit NO.0392 under wash conditions of 125 mM sodium phosphate (pH7.2), 0.05 mM EDTA, and 2.5% SDS at 65 °C. Moreover, Applicants claim in Claim 64 an isolated polynucleotide comprising a member selected from the group consisting of: (a) a polynucleotide which is at least 85% identical to the polynucleotide of (i) or (ii); and (b) a variant of the polynucleotide of (i) or (ii); wherein (i) is a polynucleotide encoding the polypeptide consisting of the amino acid sequence as set forth in SEQ ID NO:2; or (ii) is a polynucleotide encoding a mature polypeptide having the amino acid sequence expressed by the cDNA contained in CGMCC Deposit NO.0392.

The Examiner notes that NCI/CGAP teaches a nucleic acid sequence (nucleotides 1-452) that is capable of hybridizing to the polynucleotide that encodes the polypeptide as set forth in SEQ ID NO:2.

However, NCI-CGAP first fails to teach (Claim 34) an isolated polynucleotide encoding the polypeptide consisting of the amino acid sequence as set forth in SEQ ID NO:2; or an isolated polynucleotide encoding a mature polypeptide of the amino acid sequence expressed by the cDNA contained in CGMCC Deposit NO.0392. NCI/CGAP also fails to teach (Claim 51) a polynucleotide capable of hybridizing to (a) a polynucleotide encoding the polypeptide consisting of the amino acid sequence as set forth in SEQ ID NO:2; or (b) a polynucleotide encoding a mature polypeptide having the amino acid sequence expressed by the cDNA contained in CGMCC Deposit NO.0392 under a specific wash conditions of 125 mM sodium phosphate (pH7.2), 0.05 mM

EDTA, and 2.5% SDS at 65 °C. Furthermore, NCI/CGAP fails to teach (Claim 64) an isolated polynucleotide which is at least 85% identical to the polynucleotide of (i) or (ii); or a variant of the isolated polynucleotide of (i) or (ii); wherein (i) is a polynucleotide encoding the polypeptide consisting of the amino acid sequence as set forth in SEQ ID NO:2; and (ii) is a polynucleotide encoding a mature polypeptide having the amino acid sequence expressed by the cDNA contained in CGMCC Deposit NO.0392.

Moreover, as noted by the Examiner, NCI/CGAP further fails to teach expression vectors, host cells or a method of producing a polypeptide.

The deficiencies of NCI/CGAP are not overcome by the secondary references of Hillier et al. and Sibson et al.

Hillier et al. teach a polynucleotide of a length of 427 nucleotides, and only a portion of the polynucleotide sequence (nucleotides 60-356) encoding the polypeptide as set forth in SEQ ID NO:2. However, Hillier et al., like NCI/CGAP, do not teach Applicants' claimed isolated polynucleotide encoding the polypeptide consisting of the amino acid sequence as set forth in SEQ ID NO:2; nor Applicants' claimed isolated polynucleotide encoding a mature polypeptide of the amino acid sequence expressed by the cDNA contained in CGMCC Deposit NO.0392. Furthermore, Hillier et al. fail to teach a polynucleotide capable of hybridizing to (a) a polynucleotide encoding the polypeptide consisting of the amino acid sequence as set forth in SEQ ID NO:2; or (b) a polynucleotide encoding a mature polypeptide having the amino acid sequence expressed by the cDNA contained in CGMCC Deposit NO.0392 under certain wash conditions. In addition, Hillier et al., like NCI/CGAP, further fails to teach expression vectors, host cells or a method of producing a polypeptide.

Hillier et al.'s reference teaches away from Applicants' claimed invention. Hillier et al. teach a full length nucleotide sequence of 427 nucleotides (Genbank Accession No. AA455042), which encodes a polypeptide of 152 amino acids, instead of Applicants' claimed isolated polynucleotide encoding the polypeptide consisting of the amino acid sequence as set forth in SEQ ID NO:2 (99 amino acids); or isolated polynucleotide encoding a mature polypeptide having the amino acid sequence expressed by the cDNA contained in CGMCC Deposit NO.0392. There is no reason for one skilled in the art to select one specific portion (from 60 to 356, a total of 296

nucleotides) from Hillier et al.'s sequence of 427 nucleotides to encode Applicants' 99 amino acid sequence of SEQ ID NO:2.

The deficiencies of NCI/CGAP and Hillier et al. are not overcome by Sibson et al. Sibson et al. fail to teach any of Applicants' claimed isolated polynucleotide defined by Claims 34, 51 and 64. Instead, Sibson et al. merely teach that in general one can place a desired cDNA sequence into an expression vector, host cell and express the encoded protein.

Applicants respectfully point out that Applicants' claimed vector, host cells, and method of producing a chemokine-like factor polypeptide are dependent claims of Claims 34, 51 and 64 which define Applicants' claimed isolated specific polynucleotide. Furthermore, as the Examiner stated "Sibson et al. discloses that it is generally useful to place a desired cDNA sequence into an expression vector, host cell and express the encoded protein". Such a general teachings of Sibson et al. amount to nothing more than an invitation to experiment.

The Examiner alleges that it would be obvious to one skilled in the art to combine NCI-CGAP's and Hillier et al.'s cDNA and Sibson et al.'s general teaching of vector, host cell, method of expressing and isolation of expressed polypeptide to obtain Applicants' claimed invention. Applicants respectfully disagree. First, NCI-CGAP does not teach Applicants' claimed polynucleotide which encodes the polypeptide of SEQ ID NO:2. Second, as stated above, there is no reason for one skilled in the art to pick and choose 296 nucleotides from Hillier et al's 427 nucleotide sequence to obtain Applicants' claimed polynucleotide which encodes the polypeptide consisting of 99 amino acid sequence of SEQ ID NO:2. Therefore, based on the prior art teachings, one skilled in the art would not be motivated to try to combine NCI-CGAP's and Hillier et al.'s teachings with Sibson et al's reference, as suggested by the Examiner, to obtain Applicants' claimed polynucleotide which encodes the polypeptide consisting of the amino acid sequence of SEQ ID NO:2. It appears that the Examiner is attempting to use hindsight to reconstruct Applicants' claimed invention.

Furthermore, even if one combines the reference teachings as suggested by the Examiner, for example, combining Hillier et al.'s 427 nucleotide sequence with Sibson

et al.'s teaching, one would not obtain Applicant's claimed polynucleotide which encodes the polypeptide consisting of 99 amino acid sequence of SEQ ID NO:2.

Therefore, Applicant firmly believes that Applicant's claimed invention is unobvious in view of the prior art. Accordingly, Applicant respectfully requests withdrawal of the rejection based upon 35 U.S.C. §103(a).

It is respectfully submitted that Claims 34-72, the remaining pending claims, are now in condition for allowance and such action is respectfully submitted. Applicants' Agent respectfully requests a telephone interview with the Examiner with a view toward any further action deemed necessary to place the application in final condition for allowance.

Respectfully submitted,

11/30/2002
Date of Signature

By: _____
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AMENDMENTS MARKED TO SHOW CHANGES

In The Specification

A. On page 1, please amend the title of the instant application to:

[CHEMOKINE-LIKE FACTORS (CKLFS) WITH CHEMOTACTIC AND HEMATOPOIETIC STIMULATING ACTIVITIES] NUCLEIC ACID MOLECULE ENCODING CHEMOKINE-LIKE FACTOR 1 (CKLF1)

B. On page 9, please amend the fourth paragraph to:

The deposits(s) referred to herein will be maintained at the China Committee For Culture Collection of Microorganisms, General Microbiological Culture Center, Zhongguancun, Beijing, China 100080 (Name and Address of Depository) under the terms of the Budapest Treaty on the International Recognition of the Deposit of Micro-organisms for purposes of Patent Procedure. These deposits are "provided" merely as a convenience to those skill in the art and are not an admission that a deposit is required under 35 U.S.C. §112. The sequence of the polynucleotides contained in the deposited materials, as well as reference and are controlling in the event of any conflict with any description of sequences herein. A license may be required to make, use or sell the deposited materials, and no such license is hereby granted.

C. On page 22, please amend the paragraph prior to the last paragraph to:

The DNA sequence is shown in SEQ ID NO: 1. The encoding sequence was assembled by overlapping ESTs (Express Sequence Tags) provided by the EST Assembly Machine [(http:// www.tigen.it)]. The accession number of EST fragments used for the CKLF1 assembly were W38899, N95062., AA429945, AA987264, AA927461, W19056, N89912, AA516431, AA479657, AA455042, AA989129, W52820. The obtained full-length cDNA of CKLF1 has 534 base pair nucleotides, including a

poly(A) tail and a polyadenylation signal ATTAAA. The open reading frame of CKLF1 is from nucleotide 152 to nucleotide 448 as showed in SEQ ID NO:1, which encodes a polypeptide which has 99 amino acid residues. The homology analysis was conducted through GenBank on World Wide Web [(http://www.ncbi.nih.gov)]. The GenBank access (registration) number of CKLF1 is AF096895.

D. On page 22, please amend the last paragraph to:

The characteristics of CKLF1 amino acid (as set forth in SEQ ID NO: 2) were analyzed with softwares PcGene, Prosite and Signal P server provided by the World Wide Web site [(http://www.cbs.dtu.dk/services/signa- IP)]. The result shows there is a CC motif in CKLF1 amino acid, which is characteristic of the C--C chemokine subfamily. The first amino acid residue of the deduced mature polypeptide is glycine. The deduced CKLF1 protein has no typical signal cleavage site, no transmembrane domain, no DNA binding site and no putative N-glycosylation site. The first 17 amino acid residues of the N-terminal are hydrophobic and are the possible signal peptide. The homology analysis showed that the CKLF1 polypeptide shares no obvious homology with known proteins; amino acid 35 through 79 shares 46 percent homology with the permease of Caenorhabditis elegans.

E. On page 23, please amend the second paragraph to:

The 5' oligonucleotide primer 1 (P1, SEQ ID NO: 9) and 3'oligonucleotide primer 2 (P2, SEQ ID NO: 10) were designed according to the coding sequence of the CKLF1 polynucleotide. The sequences are shown as follows: P1, SEQ ID NO: 9: 5'ATG GAT AAC GTG CAG CCG AAA AT 3', P2, SEQ ID NO: 10: 5'CCG CTC GAG TTA CAA AAC TTC TTT TTT TTC 3'.

F. On page 24, please amend the paragraph prior to the last paragraph to:

The 5' oligonucleotide primer 1'_(P1', SEQ ID NO: 11) and the 3' oligonucleotide primer 2'_(P2', SEQ ID NO: 12) were designed according to the cDNA sequence of CKLF1. The 3' primer contains a complementary sequence to the XhoII site. The primers are as follows:

P1', SEQ ID NO: 11: 5'CTG ATA CCA GAA ACC ACA ACA TT 3'

P2', SEQ ID NO: 12: 5'GGA AGA ATA CAG AAA TAT GTT TAA TAC 3'

G. On page 25, please amend the paragraph prior to the last paragraph to:

The coding regions of CKLF1, 2 and 4 were amplified by using primer 1 (P1) and primer 5 (P5, SEQ ID NO: 13: 5' CGG GAT CCA AAA CTT CTT TTT TTT CAT GC 3'). In the coding region of CKLF1, 2 and 4, the stop codon was removed and a BamHI site was introduced near the 3' end. The PCR products were blunted by klenow enzyme and then digested with BamHI. The pEGFP-N1 expression vector (CLOTECH) was digested with EcoRI, blunted with klenow enzyme and then digested with BamHI. After purification and recovery from the agarose gels, the fragments were ligated into the digested vectors. The recombinant plasmids were designated pEGFP-CKLF1, 2 and 4, respectively. The coding sequences of CKLF1, 2 and 4 were the same as the open reading frame of EGFP.